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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 13 June 2001 (13.06.01)	
International application No. PCT/CA00/01132	Applicant's or agent's file reference DH/12554.10
International filing date (day/month/year) 21 September 2000 (21.09.00)	Priority date (day/month/year) 21 September 1999 (21.09.99)
Applicant CHANDRASEKAR, Baskaran et al	

1. The designated Office is hereby notified of its election made:

☒

in the demand filed with the International Preliminary Examining Authority on:

18 April 2001 (18.04.01)

☐

in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was☐

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

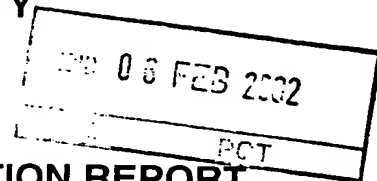
Claudio Borton

Telephone No.: (41-22) 338.83.38

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)





Applicant's or agent's file reference DH/12554.10		FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA00/01132	International filing date (day/month/year) 21/09/2000	Priority date (day/month/year) 21/09/1999	
International Patent Classification (IPC) or national classification and IPC A61K31/00			
Applicant INSTITUT DE CARDIOLOGIE DE MONTREAL et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 18/04/2001	Date of completion of this report 04.02.02
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Sindel, U Telephone No. +49 89 2399 7064 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/01132

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-40 as originally filed

Claims, No.:

1-8 as received on 20/12/2001 with letter of 18/12/2001

Drawings, sheets:

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☒ the claims, Nos.: 1-9

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA00/01132

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations
see separate sheet

Section V

The subject matter of claims 1-8 of the present application is regarded as being new and inventive since the claimed use of 17- β -estradiol for the manufacture of a medicament for improved reendothelization in an injured blood vessel has not been described so far.

Nevertheless the applicant is informed that the claimed use of 17- β -estradiol for the manufacture of a medicament to improve the vascular endothelial function is redundant.

WHAT IS CLAIMED IS:

1. The use of 17- β estradiol or a derivative thereof in the making of a medication, for *in-situ* administration in the lumen of a blood vessel having suffered vascular injury, at the injured site, to prevent vascular intima hyperplasia, or for improving vascular endothelium function, or both, in a patient.
2. An anti-restenotic composition for in-situ administration in the lumen of a blood vessel having suffered vascular injury, at the injured site, which comprises an effective amount of 17- β estradiol or a derivative thereof in a pharmaceutically acceptable carrier.
3. A device comprising 17- β estradiol or a derivative thereof for in-situ delivery of an anti-restenotic amount thereof to a vascular site having suffered vascular injury.
4. The use as defined in claim 1, or the composition as defined in claim 2, or the device of claim 3, wherein 17- β estradiol or a derivative thereof is present in a dose unit of 1 to 5000 $\mu\text{g/Kg}$ of patient's body weight.
5. The use, as defined in claim 1, or the composition as defined in claim 2, or the device of claim 3, wherein 17- β estradiol or a derivative thereof is present in a dose unit of 10 to 50 $\mu\text{g/Kg}$ of patient's body weight.
6. The use as defined in claim 1, or the composition as defined in claim 2, or the device of claim 3, wherein 17- β estradiol or a

derivative thereof is present in a dose unit of 10 to 30 $\mu\text{g/Kg}$ Kg of patient's body weight.

7. The use or the composition as defined in any one of
5 claims 1, 2 and 4 to 6 wherein said pharmaceutically acceptable carrier comprises hydroxypropyl-beta-cyclodextrin (HPCD).

8. The use or the composition as defined in claim 7,
wherein HPCD is present in a dose capable of solubilizing 17-beta estradiol
10 or a derivative thereof.

9. The use or the composition as defined in Claim 6, where
17-beta-estradiol or a derivative thereof is admixed with a carrier comprising
at least 0.63 mg hydroxypropyl-beta-cyclodextrin per kilogram of patient's
15 body weight.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 March 2001 (29.03.2001)

PCT

(10) International Publication Number
WO 01/21157 A3

- (51) International Patent Classification⁷: **A61K 31/565**, A61P 41/00
- (21) International Application Number: PCT/CA00/01132
- (22) International Filing Date:
21 September 2000 (21.09.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
2,282,982 21 September 1999 (21.09.1999) CA
2,300,246 9 March 2000 (09.03.2000) CA
- (71) Applicant (for all designated States except US): **INSTITUT DE CARDIOLOGIE DE MONTREAL [CA/CA]**; 5000 Bélanger Street East, Montreal, Quebec H1T 1C8 (CA).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **CHAN-DRASEKAR, Baskaran [IN/IN]**; 2, Justice Ramanujam Road, Dr. Radhakrishnan Nagar, Chennai 600 041 (IN). **TANGUAY, Jean-François [CA/CA]**; C.P. 323, succ. Mont-Royal, Monreal, Quebec H3P 3C5 (CA).
- (74) Agents: **DUBUC, Jean, H. et al.**; Goudreau Gage Dubuc, The Stock Exchange Tower, Suite 3400, 800 Place Victoria, P.O. Box 242, Montreal, Quebec H4Z 1E9 (CA).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- (88) Date of publication of the international search report:
13 December 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LOCAL DELIVERY OF 17-BETA ESTRADIOL FOR PREVENTING VASCULAR INTIMA HYPERPLASIA AND FOR IMPROVING VASCULAR ENDOTHELIUM FUNCTION AFTER VASCULAR INJURY

(57) Abstract: The cardioprotective effects of estrogen are well recognized. In *in vitro* experiments, and upon systemic administration, 17-beta estradiol has shown to inhibit vascular smooth muscle cell proliferation and intima hyperplasia and to improve vascular endothelium function, after vascular injury. We hypothesized that locally delivered 17-beta estradiol could prevent restenosis. Compositions are use of 17-beta estradiol for *in-situ* administration at a vascular injured site are objects of the present invention.

WO 01/21157 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/565 A61P41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, MEDLINE, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 56312 A (SCIMED LIFE SYSTEMS INC) 17 December 1998 (1998-12-17) abstract page 7, line 5-17 page 8, line 11-18; claims 1,8,9 ---	1-6
X	YOON YOUNG-SUP ET AL: "Local intraluminal infusion of oestradiol containing liposome in rat cartoid balloon injury model." EUROPEAN HEART JOURNAL, vol. 19, no. ABST. SUPPL., August 1998 (1998-08), page 616 XP001014473 XXth Congress of the European Society of Cardiology;Vienna, Austria; August 22-26, 1998 ISSN: 0195-668X abstract --- -/--	1-6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

10 September 2001

Date of mailing of the international search report

24/09/2001

Name and mailing address of the ISA

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 NL - 2280 HV Rijswijk
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Authorized officer

A. Jakobs

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHANG Y-Q ET AL: "EFFECTS OF GENDER AND ESTRADIOL TREATMENT ON FOCAL BRAIN ISCHEMIA" BRAIN RESEARCH, AMSTERDAM, NL, vol. 784, no. 1/2, 16 February 1998 (1998-02-16), pages 321-324, XP000884355 ISSN: 0006-8993 abstract page 322, column 1, paragraph 2; figure 2; table 1 page 323, column 2, paragraph 2 -page 324, column 1, paragraph 2 ---	1-9
X	KAUFFMAN RAYMOND F ET AL: "Comparative effects of local vs. systemic administration of estrogen upon vascular responses to balloon injury." CIRCULATION, vol. 92, no. 8 SUPPL., 1995, page I628 XP001014766 68th Scientific Session of the American Heart Association; Anaheim, California, USA; November 13-16, 1995 ISSN: 0009-7322 abstract ---	1-6
Y	---	7-9
Y	US 5 376 652 A (JAVITT NORMAN B) 27 December 1994 (1994-12-27) abstract column 3, line 5-9 column 4, line 29-50 ---	7-9
X	US 5 866 561 A (UNGS MARK T) 2 February 1999 (1999-02-02) abstract column 1, line 65 -column 2, line 46 column 4, line 10,11; claims 1-8 ---	1-6
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 1999 (1999-05) PERROT-APPLANAT M: "Estradiol and proliferation of vascular cells." Database accession no. PREV200000507148 XP002177140 abstract & THERAPIE (LONDON), vol. 54, no. 3, May 1999 (1999-05), pages 333-337, ISSN: 0040-5957 --- -/--	1-6

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995 MIKKOLA TOMI ET AL: "17-beta-estradiol stimulates prostacyclin, but not endothelin-1, production in human vascular endothelial cells." Database accession no. PREV199598355996 XP002177141 abstract & JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 80, no. 6, 1995, pages 1832-1836, ISSN: 0021-972X</p> <p style="text-align: center;">---</p>	1-6
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 MIKKOLA TOMI ET AL: "Effect of physiological concentrations of estradiol on PGI-2 and NO in endothelial cells." Database accession no. PREV199799286811 XP002177142 abstract & MATURITAS, vol. 25, no. 2, 1996, pages 141-147, ISSN: 0378-5122</p> <p style="text-align: center;">---</p>	1-6
X,P	<p>WO 00 12147 A (SCIMED LIFE SYSTEMS INC) 9 March 2000 (2000-03-09) abstract page 4, line 29 -page 5, line 15 page 10, line 8-23 page 12, line 21-27; claims 1,11</p> <p style="text-align: center;">---</p>	1-6
X,P	<p>WO 00 10552 A (GLOBAL VASCULAR CONCEPTS INC) 2 March 2000 (2000-03-02) abstract page 1, line 10-14 page 3, line 1 -page 4, line 2; claims 1-13</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-6

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHANDRASEKAR, BASKARAN (1) ET AL: "Coronary artery endothelial protection following local delivery of 17-beta estradiol during balloon angioplasty: A potential new pharmacological approach to improve long-term outcome of angioplasty." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY., (FEB., 2000) VOL. 35, NO. 2 SUPPL. A, PP. 58A. MEETING INFO.: 29TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY. ANAHEIM, CALIFORNIA, USA MARCH 12-15, 2000 , XP001015229 abstract	1-6
X	--- SELZMAN, CRAIG H. ET AL: "Estrogen replacement inhibits intimal hyperplasia and the accumulation and effects of transforming growth factor.beta.1" J. SURG. RES. (1998), 80(2), 380-385 , XP001014759 abstract	1-6
A	--- KEANEY J F ET AL: "17BETA-ESTRADIOL PRESERVES ENDOTHELIAL VASODILATOR FUNCTION AND LIMITS LOW-DENSITY LIPOPROTEIN OXIDATION IN HYPERCHOLESTEROLEMIC SWINE" CIRCULATION, AMERICAN HEART ASSOCIATION, DALLAS, TX, US, vol. 89, no. 5, May 1994 (1994-05), pages 2251-2259, XP001014735 ISSN: 0009-7322 the whole document	1-6
A	--- DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 KUBLIK HEIKE ET AL: "Nasal absorption of 17-beta-estradiol from different cyclodextrin inclusion formulations in sheep." Database accession no. PREV199799383935 XP002177143 abstract & EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 42, no. 6, 1996, pages 320-324, ISSN: 0939-6411 -----	7-9

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

In view of the wording of claims 1-9 presently on file, in as far as the expression "derivative of 17-beta estradiol" is concerned, which renders it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely the use of and compositions/devices comprising 17-beta estradiol.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 00/01132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9856312 A	17-12-1998	NONE	
US 5376652 A	27-12-1994	AU 682084 B	18-09-1997
		AU 1256895 A	19-06-1995
		CA 2177822 A	08-06-1995
		EP 0730457 A	11-09-1996
		JP 9506091 T	17-06-1997
		WO 9515165 A	08-06-1995
		US 5587368 A	24-12-1996
US 5866561 A	02-02-1999	US 6149641 A	21-11-2000
WO 0012147 A	09-03-2000	EP 1119379 A	01-08-2001
WO 0010552 A	02-03-2000	AU 5687199 A	14-03-2000



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference DH/12554.10	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/CA 00/ 01132	International filing date (day/month/year) 21/09/2000	(Earliest) Priority Date (day/month/year) 21/09/1999
Applicant INSTITUT DE CARDIOLOGIE DE MONTREAL		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

In view of the wording of claims 1-9 presently on file, in as far as the expression "derivative of 17-beta estradiol" is concerned, which renders it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely the use of and compositions/devices comprising 17-beta estradiol.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/01132

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/565 A61P41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, MEDLINE, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 56312 A (SCIMED LIFE SYSTEMS INC) 17 December 1998 (1998-12-17) abstract page 7, line 5-17 page 8, line 11-18; claims 1,8,9 ---	1-6
X	YOON YOUNG-SUP ET AL: "Local intraluminal infusion of oestradiol containing liposome in rat cartoid balloon injury model." EUROPEAN HEART JOURNAL, vol. 19, no. ABST. SUPPL., August 1998 (1998-08), page 616 XP001014473 XXth Congress of the European Society of Cardiology;Vienna, Austria; August 22-26, 1998 ISSN: 0195-668X abstract ---	1-6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

10 September 2001

Date of mailing of the international search report

24/09/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

A. Jakobs

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ZHANG Y-Q ET AL: "EFFECTS OF GENDER AND ESTRADIOL TREATMENT ON FOCAL BRAIN ISCHEMIA" BRAIN RESEARCH, AMSTERDAM, NL, vol. 784, no. 1/2, 16 February 1998 (1998-02-16), pages 321-324, XP000884355 ISSN: 0006-8993 abstract page 322, column 1, paragraph 2; figure 2; table 1 page 323, column 2, paragraph 2 -page 324, column 1, paragraph 2 ---</p>	1-9
X	<p>KAUFFMAN RAYMOND F ET AL: "Comparative effects of local vs. systemic administration of estrogen upon vascular responses to balloon injury." CIRCULATION, vol. 92, no. 8 SUPPL., 1995, page I628 XP001014766 68th Scientific Session of the American Heart Association; Anaheim, California, USA; November 13-16, 1995 ISSN: 0009-7322 abstract ---</p>	1-6
Y	abstract	7-9
Y	<p>US 5 376 652 A (JAVITT NORMAN B) 27 December 1994 (1994-12-27) abstract column 3, line 5-9 column 4, line 29-50 ---</p>	7-9
X	<p>US 5 866 561 A (UNGS MARK T) 2 February 1999 (1999-02-02) abstract column 1, line 65 -column 2, line 46 column 4, line 10,11; claims 1-8 ---</p>	1-6
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 1999 (1999-05) PERROT-APPLANAT M: "Oestradiol and proliferation of vascular cells." Database accession no. PREV200000507148 XP002177140 abstract & THERAPIE (LONDON), vol. 54, no. 3, May 1999 (1999-05), pages 333-337, ISSN: 0040-5957 --- -/--</p>	1-6

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995 MIKKOLA TOMI ET AL: "17-beta-estradiol stimulates prostacyclin, but not endothelin-1, production in human vascular endothelial cells." Database accession no. PREV199598355996 XP002177141 abstract & JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 80, no. 6, 1995, pages 1832-1836, ISSN: 0021-972X</p> <p>---</p>	1-6
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 MIKKOLA TOMI ET AL: "Effect of physiological concentrations of estradiol on PGI-2 and NO in endothelial cells." Database accession no. PREV199799286811 XP002177142 abstract & MATURITAS, vol. 25, no. 2, 1996, pages 141-147, ISSN: 0378-5122</p> <p>---</p>	1-6
X,P	<p>WO 00 12147 A (SCIMED LIFE SYSTEMS INC) 9 March 2000 (2000-03-09) abstract page 4, line 29 -page 5, line 15 page 10, line 8-23 page 12, line 21-27; claims 1,11</p> <p>---</p>	1-6
X,P	<p>WO 00 10552 A (GLOBAL VASCULAR CONCEPTS INC) 2 March 2000 (2000-03-02) abstract page 1, line 10-14 page 3, line 1 -page 4, line 2; claims 1-13</p> <p>---</p> <p style="text-align: center;">-/--</p>	1-6

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	CHANDRASEKAR, BASKARAN (1) ET AL: "Coronary artery endothelial protection following local delivery of 17-beta estradiol during balloon angioplasty: A potential new pharmacological approach to improve long-term outcome of angioplasty." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY., (FEB., 2000) VOL. 35, NO. 2 SUPPL. A, PP. 58A. MEETING INFO.: 29TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY. ANAHEIM, CALIFORNIA, USA MARCH 12-15, 2000 , XP001015229 abstract	1-6
X	SELZMAN, CRAIG H. ET AL: "Estrogen replacement inhibits intimal hyperplasia and the accumulation and effects of transforming growth factor.beta.1" J. SURG. RES. (1998), 80(2), 380-385 , XP001014759 abstract	1-6
A	KEANEY J F ET AL: "17BETA-ESTRADIOL PRESERVES ENDOTHELIAL VASODILATOR FUNCTION AND LIMITS LOW-DENSITY LIPOPROTEIN OXIDATION IN HYPERCHOLESTEROLEMIC SWINE" CIRCULATION, AMERICAN HEART ASSOCIATION, DALLAS, TX, US, vol. 89, no. 5, May 1994 (1994-05), pages 2251-2259, XP001014735 ISSN: 0009-7322 the whole document	1-6
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 KUBLIK HEIKE ET AL: "Nasal absorption of 17-beta-estradiol from different cyclodextrin inclusion formulations in sheep." Database accession no. PREV199799383935 XP002177143 abstract & EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 42, no. 6, 1996, pages 320-324, ISSN: 0939-6411	7-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 00/01132

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9856312	A	17-12-1998	NONE	
US 5376652	A	27-12-1994	AU 682084 B	18-09-1997
			AU 1256895 A	19-06-1995
			CA 2177822 A	08-06-1995
			EP 0730457 A	11-09-1996
			JP 9506091 T	17-06-1997
			WO 9515165 A	08-06-1995
			US 5587368 A	24-12-1996
US 5866561	A	02-02-1999	US 6149641 A	21-11-2000
WO 0012147	A	09-03-2000	EP 1119379 A	01-08-2001
WO 0010552	A	02-03-2000	AU 5687199 A	14-03-2000

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:
GOUDREAU GAGE DUBUC
The Stock Exchange Tower
Attn. DUBUC, Jean H.
800 Place Victoria, Suite 3400
P.O. Box 242
Montréal, Quebec H4Z 1E9
CANADA

Date of mailing
(day/month/year)

24/09/2001

Applicant's or agent's file reference
DH/12554.10

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/CA 00/01132

International filing date
(day/month/year) 21/09/2000

Applicant

INSTITUT DE CARDIOLOGIE DE MONTREAL

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Joannes Vergoosen

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference DH/12554.10	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/CA 00/ 01132	International filing date (day/month/year) 21/09/2000	(Earliest) Priority Date (day/month/year) 21/09/1999
Applicant INSTITUT DE CARDIOLOGIE DE MONTREAL		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

National Application No

PCT/CA 00/01132

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/565 A61P41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, MEDLINE, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X D ₂	WO 98 56312 A (SCIMED LIFE SYSTEMS INC) 17 December 1998 (1998-12-17) abstract page 7, line 5-17 page 8, line 11-18; claims 1,8,9 ---	1-6
X D ₁	YOON YOUNG-SUP ET AL: "Local intraluminal infusion of oestradiol containing liposome in rat cartoid balloon injury model." EUROPEAN HEART JOURNAL, vol. 19, no. ABST. SUPPL., August 1998 (1998-08), page 616 XP001014473 XXth Congress of the European Society of Cardiology;Vienna, Austria; August 22-26, 1998 ISSN: 0195-668X abstract ---	1-6

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

10 September 2001

Date of mailing of the international search report

24/09/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

A. Jakobs

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>D3</p> <p>ZHANG Y-Q ET AL: "EFFECTS OF GENDER AND ESTRADIOL TREATMENT ON FOCAL BRAIN ISCHEMIA" BRAIN RESEARCH, AMSTERDAM, NL, vol. 784, no. 1/2, 16 February 1998 (1998-02-16), pages 321-324, XP000884355 ISSN: 0006-8993 abstract page 322, column 1, paragraph 2; figure 2; table 1 page 323, column 2, paragraph 2 -page 324, column 1, paragraph 2</p>	1-9
X	<p>KAUFFMAN RAYMOND F ET AL: "Comparative effects of local vs. systemic administration of estrogen upon vascular responses to balloon injury." CIRCULATION, vol. 92, no. 8 SUPPL., 1995, page I628 XP001014766 68th Scientific Session of the American Heart Association; Anaheim, California, USA; November 13-16, 1995 ISSN: 0009-7322</p>	1-6
Y	<p>abstract</p>	7-9
Y	<p>US 5 376 652 A (JAVITT NORMAN B) 27 December 1994 (1994-12-27) abstract column 3, line 5-9 column 4, line 29-50</p>	7-9
X	<p>US 5 866 561 A (UNGS MARK T) 2 February 1999 (1999-02-02) abstract column 1, line 65 -column 2, line 46 column 4, line 10,11; claims 1-8</p>	1-6
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 1999 (1999-05) PERROT-APPLANAT M: "Qestradiol and proliferation of vascular cells." Database accession no. PREV200000507148 XP002177140 abstract & THERAPIE (LONDON), vol. 54, no. 3, May 1999 (1999-05), pages 333-337, ISSN: 0040-5957</p>	1-6

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995 MIKKOLA TOMI ET AL: "17-beta-estradiol stimulates prostacyclin, but not endothelin-1, production in human vascular endothelial cells." Database accession no. PREV199598355996 XP002177141 abstract & JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 80, no. 6, 1995, pages 1832-1836, ISSN: 0021-972X</p>	1-6
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 MIKKOLA TOMI ET AL: "Effect of physiological concentrations of estradiol on PGI-2 and NO in endothelial cells." Database accession no. PREV199799286811 XP002177142 abstract & MATURITAS, vol. 25, no. 2, 1996, pages 141-147, ISSN: 0378-5122</p>	1-6
X,P	<p>WO 00 12147 A (SCIMED LIFE SYSTEMS INC) 9 March 2000 (2000-03-09) abstract page 4, line 29 -page 5, line 15 page 10, line 8-23 page 12, line 21-27; claims 1,11</p>	1-6
X,P	<p>WO 00 10552 A (GLOBAL VASCULAR CONCEPTS INC) 2 March 2000 (2000-03-02) abstract page 1, line 10-14 page 3, line 1 -page 4, line 2; claims 1-13</p>	1-6

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	CHANDRASEKAR, BASKARAN (1) ET AL: "Coronary artery endothelial protection following local delivery of 17-beta estradiol during balloon angioplasty: A potential new pharmacological approach to improve long-term outcome of angioplasty." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY., (FEB., 2000) VOL. 35, NO. 2 SUPPL. A, PP. 58A. MEETING INFO.: 29TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY. ANAHEIM, CALIFORNIA, USA MARCH 12-15, 2000 , XP001015229 abstract	1-6
X	SELZMAN, CRAIG H. ET AL: "Estrogen replacement inhibits intimal hyperplasia and the accumulation and effects of transforming growth factor.beta.1" J. SURG. RES. (1998), 80(2), 380-385 , XP001014759 abstract	1-6
A	KEANEY J F ET AL: "17BETA-ESTRADIOL PRESERVES ENDOTHELIAL VASODILATOR FUNCTION AND LIMITS LOW-DENSITY LIPOPROTEIN OXIDATION IN HYPERCHOLESTEROLEMIC SWINE" CIRCULATION, AMERICAN HEART ASSOCIATION, DALLAS, TX, US, vol. 89, no. 5, May 1994 (1994-05), pages 2251-2259, XP001014735 ISSN: 0009-7322 the whole document	1-6
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 KUBLIK HEIKE ET AL: "Nasal absorption of 17-beta-estradiol from different cyclodextrin inclusion formulations in sheep." Database accession no. PREV199799383935 XP002177143 abstract & EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 42, no. 6, 1996, pages 320-324, ISSN: 0939-6411	7-9

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

In view of the wording of claims 1-9 presently on file, in as far as the expression "derivative of 17-beta estradiol" is concerned, which renders it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely the use of and compositions/devices comprising 17-beta estradiol.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/01132

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 00/01132

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9856312	A	17-12-1998	NONE		
US 5376652	A	27-12-1994	AU	682084 B	18-09-1997
			AU	1256895 A	19-06-1995
			CA	2177822 A	08-06-1995
			EP	0730457 A	11-09-1996
			JP	9506091 T	17-06-1997
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US 5866561	A	02-02-1999	US	6149641 A	21-11-2000
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WO 0010552	A	02-03-2000	AU	5687199 A	14-03-2000

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

DUBUC, Jean, H.
Goudreau Gage Dubuc
The Stock Exchange Tower
Suite 3400, 800 Place Victoria
P.O. Box 242
Montreal, Quebec H4Z 1E9
CANADA

Date of mailing (day/month/year)

29 March 2001 (29.03.01)

Applicant's or agent's file reference

DH/12554.10

IMPORTANT NOTICE

International application No.

PCT/CA00/01132

International filing date (day/month/year)

21 September 2000 (21.09.00)

Priority date (day/month/year)

21 September 1999 (21.09.99)

Applicant

INSTITUT DE CARDIOLOGIE DE MONTREAL et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU, KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EA, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU.

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 29 March 2001 (29.03.01) under No. WO 01/21157

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra

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